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Reprinted from

JOURNAL OF CHRONIC DISEASES
St. Louis

Vol. 4, No. 2, Pages 177-185, August, 1956
(Printed in the U. S. A.)

UNTREATED SYPHILIS IN THE MALE NEGRO

X. Twenty Years of Clinical Observation of Untreated Syphilitic and Presumably Nonsyphilitic Groups

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(Received for publication Nov. 5, 1955.)

THIS report summarizes the clinical status of the members of the Tuskegee study who were living and examined in the twentieth year of observation. Particular attention will be given to evidence of late syphilis in the group and to abnormalities of the cardiovascular system in the syphilitic and nonsyphilitic groups.

Eventually, a clinicopathologic correlation between syphilitic and nonsyphilitic groups will be required, but a valid final analysis will not be possible until the majority of the patients will have lived out the total life experience.

Thus far other papers of the series have discussed the adverse effect of syphilis on life expectancy,[1,2] have shown in the group coming to autopsy the pathologic changes resulting from syphilis,[3] and have, throughout the series of examinations, shown a greater amount of physiologic change, not necessarily specifically syphilitic, among the syphilitic patients.[4] The shortening of life expectancy observed in man, which can in part be explained on the basis of specific anatomic changes,[1,2] has a counterpart in the white mouse, in which animal it has been shown by Rosahn[5] that a syphilitic group has a significantly lessened life expectancy even though it has not been possible to demonstrate specific microscopic lesions of syphilis. The question has been raised as to the possible mechanisms of this adverse effect, but answers are not as yet available. Within the human group a similar shortening of life span is noted which, at least in part, can be correlated with specific, more or less lethal anatomic changes. The specific factors concerned with this shortening in syphilitic patients remain to be

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This article is one of a series on untreated syphilis in the male Negro which the Venereal Disease Program, Division of Special Health Services, plans to assemble into a monograph. Single copies of the monograph will be made available upon request to the Venereal Disease Program, Division of Special Health Services, United States Public Health Service, Washington 25, D. C.

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determined. In the present report of findings observed at the twenty-year mark, attention is given not only to the cardiovascular and nervous systems but to some general attributes of health in an attempt to elucidate the problem.

DIAGNOSIS OF SYPHILITIC HEART DISEASE

As interest in detection of early and slight cardiovascular complications in these men grew keener over the years among the various medical examiners, increasing use of the x-ray and fluoroscope was made. In 1932, chest films in the posterior-anterior view of all the men were taken at the John Andrew Memorial Hospital in Tuskegee, and these films proved a valuable base line for comparison with later ones. In subsequent physical examinations, all those examined received x-rays of the chest in multiple views (posterior-anterior, left anterior oblique, and right anterior oblique) with barium swallow. From these films it was possible to measure heart sizes (in the manner of Bordet-Vaquez and Fray), the aortic diameter at the knob, the width of the aortic arch, and to calculate the various cardiothoracic ratios. Diebert in his report in 1946[4] called attention to certain striking differences in the aortic-cardiac measurements of syphilitic compared to nonsyphilitic patients. Those x-ray measurements have been made at each examination so that data are accumulating which should reveal long-range trends in the changing size and contour of the heart and aorta as seen radiologically. During the first examination fluoroscopy was done on only a few patients suspected of aneurysm. Later fluoroscopy became routine for nonsyphilitic individuals as well as syphilitic ones. The pathologist in this study (Dr. J. J. Peters) has been studying the correlation of ante-mortem x-ray measurements with post-mortem data for future publication. In addition to chest films, x-ray studies have been made of long bones and the skull wherever necessary to confirm diagnoses of syphilitic osteitis.

X-RAY DIAGNOSIS OF SYPHILITIC HEART DISEASE

During the period of this study many radiologic criteria have been proposed for earlier or more precise diagnosis of syphilitic heart diseases. The lack of value of any of the proposed criteria based upon aortic mensuration has been adequately documented by Kemp and Cochems.[6] In this series, the unreliability of any of the criteria proposed during the twenty-year period has been shown in the group coming to autopsy. Among individuals with a history of syphilis, the diagnosis of uncomplicated syphilitic aortitis made during life was confirmed in only half of the patients, thus pointing up the inadequacy of diagnostic criteria with which it still is necessary to work. While the diagnosis of syphilitic aneurysm and of syphilitic aortic insufficiency can be made ante mortem with a relatively high degree of accuracy, it is as yet not possible to diagnose satisfactorily uncomplicated aortitis. No informative discussion of aortitis based on this study group can be prepared until the larger part of the group has come to autopsy.

X-RAY ABNORMALITIES

No attempt was made to classify abnormalities as to syphilitic etiology except for those patients known to have saccular aneurysm. Table I shows

that there is a higher degree of abnormality in the syphilitic group than in the control. Such results suggest that men with untreated syphilis may be predisposed to changes in their cardiovascular systems which readily will be recognized as abnormal by the radiologist, although he cannot categorically ascribe these changes, in part or altogether, to a syphilitic process. In other words, the question arises as to whether the majority of changes in the aorta as the result of syphilitic involvement are sufficiently distinctive to permit of accurate diagnosis during life by the techniques now available, or whether syphilis predisposes to more severe, or premature degenerative vascular disease. In one of the previous reports,[4] evidence in favor of the latter view was presented in that there were significant differences between syphilitic and nonsyphilitic patients when palpable stiffening of superficial vessels, radial, brachial, and temporal, was compared. However, validity of findings referable to palpation of vessels can be disputed because of the subjective factors involved.

TABLE I. NONSPECIFIC X-RAY ABNORMALITIES OF THE HEART AND AORTA COMPARED AMONG STILL LIVING SYPHILITIC AND NONSYPHILITIC PATIENTS

AGE GROUP	SYPHILITIC PATIENTS			NONSYPHILITIC PATIENTS			SIGNIFICANCE OF DIFFERENCE IN ABNORMALITY IN THE TWO GROUPS
	NUMBER OF PATIENTS EXAMINED	PER CENT NORMAL	PER CENT ABNORMAL	NUMBER OF PATIENTS EXAMINED	PER CENT NORMAL	PER CENT ABNORMAL	
45–49 years	26	38.5	61.5	20	90.0	10.0	$P = < .01$
50–54 years	16	56.3	43.3	16	62.5	37.5	$P = .70$
55–59 years	20	20.0	80.0	8	50.0	50.0	$P = .10$
60–64 years	10	15.8	84.2	10	70.0	30.0	$P = < .01$
65–69 years	26	15.4	84.6	16	43.8	56.2	$P = < .05$
70–74 years	15	13.3	86.7	14	35.7	64.3	$P = < .20$
75 years and over	16	6.2	93.8	8	37.5	62.5	$P = .05$
Total	138	23.9	76.1	92	58.7	41.3	$P = < .01$

BLOOD PRESSURE

In attempting to diagnose hypertensive cardiovascular disease among men ranging in age from the fifth to the ninth decades, we encountered the same problems as were described by Dublin and Marks,[7] who studied an aging insurance population, and by Gover,[8] who worked with various age groups in a rural health study. These workers found that inflexible standards of "normal" systolic and diastolic levels must be modified in order to allow for changes in blood pressure which accompany aging in the particular race and sex being studied. In meeting this problem of manometric standards, which still are being revised, the advantage of having nonsyphilitic controls from the onset of the study for comparison is apparent. Rather than to attempt a comparison of the blood pressure readings of the syphilitic patients with national averages for male Negroes of various geographic, occupational, and economic levels, we had only to compare the two groups in the study.

Fig. 1 shows the comparative percentage of syphilitic and nonsyphilitic patients having abnormal blood pressure according to the age of patients when examined in 1952. Abnormal blood pressure is defined as systolic pressure greater than 150 mm. Hg and/or diastolic pressure greater than 90 mm. Hg.

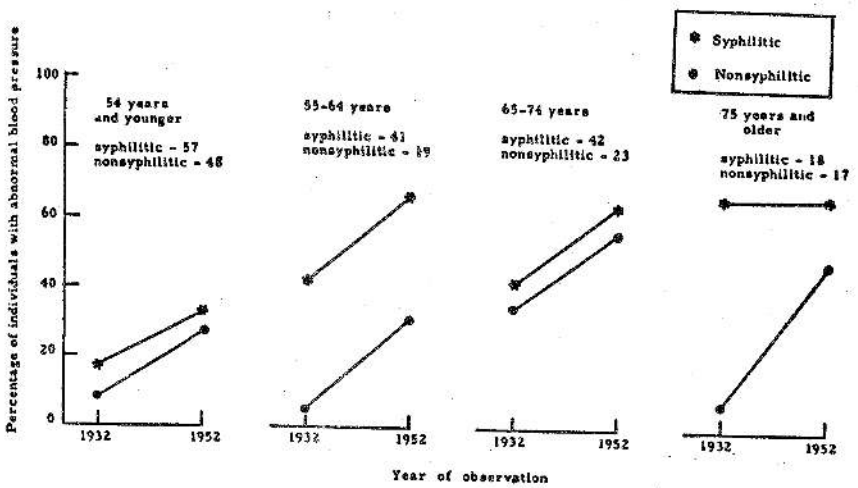

Fig. 1.—Comparative percentages of patients with abnormal blood pressure (systolic, more than 150 mm. Hg, and/or diastolic, more than 90 mm. Hg) among syphilitic and nonsyphilitic individuals examined both in 1932 and 1952, by age in 1952.

Since these percentages of abnormality are based on patients examined both in 1932 and 1952, it is apparent that there is an increasing amount of abnormality over the twenty-year span among the syphilitic and nonsyphilitic individuals in each age group. The slopes of the lines connecting the points of abnormality in 1932 and 1952 are practically identical for syphilitic and nonsyphilitic patients in the age (in 1952) intervals 34 years and younger, 35 to 44 years, and 45 to 54 years. This similarity would indicate that the slope is a true measure of the effect of aging process on the blood pressure. However, the level of the line for the syphilitic group in each of these three age groups is higher than that for the nonsyphilitic group, which would indicate a higher prevalence of blood pressure abnormality among the syphilitic patients. Since the number of patients in the last age-interval was limited to those 75 years or older when examined in 1952, the percentages are based on a small number of patients and are, therefore, not too meaningful. It is of interest, however, that among these elderly patients the same percentage of abnormality in blood pressure was found in the syphilitic group in 1932 as was found in 1952, and, for the most part, the same individuals were found to be abnormal in this respect.

ELECTROCARDIOGRAMS

As early as 1932, electrocardiograms were taken on selected patients but did not become part of the routine examination until 1938. Precordial leads have been used since 1948. In some cases serial records are available over a

twenty-year period of observation; however, in most patients they cover only the past fourteen years. From what is known of the insidious and chronic nature of syphilitic cardiovascular disease, we did not expect to obtain diagnostic electrocardiograms from the survivors. We did expect that the more advanced cases of syphilitic heart disease would show electrocardiographic evidence of cardiac hypertrophy, ventricular strain, arrhythmias, ischemic patterns, or other signs of heart damage which are nonspecific as to etiology. At the onset of the survey, we reviewed the records taken on those men who had been autopsied and for whom ante-mortem electrocardiograms were available in order to see if there was any relationship between electrocardiographic evidence of damage and pathologic changes. It was realized that the sample was small, but we were nonetheless surprised to see the lack of correlation (Table II). Despite their apparent lack of value as a screening device, ECG's were again taken routinely in the recent survey. The records were interpreted without reference to patient's syphilitic or nonsyphilitic status. Diagnosis of "abnormal record" included minor abnormalities of rhythm and axis deviation. These diagnoses were made by one of us (S.H.S.) who had only a general background in record interpretation; frequent consultations with the Veterans Administration hospital cardiologist were held. Our conservative policy was to require obvious evidence before calling any record abnormal. The patients with syphilis (Table II) not only had more abnormal records than the nonsyphilitic individuals but this difference was found to be statistically significant.

TABLE II. COMPARISON OF ABNORMAL ELECTROCARDIOGRAMS

A. Among Syphilitic and Nonsyphilitic Patients Later Examined at Autopsy

PATIENT STATUS	NUMBER OF PATIENTS EXAMINED POST MORTEM	ECG INTERPRETATION PRIOR TO DEATH			
		NORMAL		ABNORMAL	
		NUMBER	PER CENT	NUMBER	PER CENT
Syphilitic	23	19	82.6	4	17.4
Nonsyphilitic	8	2	25.0	6	75.0

B. Among Living Syphilitic and Nonsyphilitic Patients

PATIENT STATUS	NUMBER OF PATIENTS EXAMINED	ECG INTERPRETATION			
		NORMAL		ABNORMAL	
		NUMBER	PER CENT	NUMBER	PER CENT
Syphilitic	152	101	66.4	51	33.6
Nonsyphilitic	93	74	79.6	19	20.4

might be evaluated differently by physicians using somewhat different criteria. Only comparable data, therefore, are included. Furthermore, these abnormalities were recorded as the men were examined, without bias or knowledge of the patient's syphilitic or nonsyphilitic status. In Table III, "cardiac—chief complaint" refers to whether the patient volunteered some pertinent symptom referable to the cardiovascular system as his chief or presenting complaint. This includes severe intermittent claudication of the extremities, angina, dyspnea, orthopnea, severe palpitation, or syncope.

However, if the patient insisted that some other symptom was more troublesome than cardiac symptoms, then he was not included in this group.

"Cardiac enlargement" includes findings from both fluoroscopic and x-ray examinations. In borderline cases where disagreements occurred in interpretation of findings, the diagnoses of physicians who had previously examined the patient were given consideration.

"Arteriosclerosis" includes evidence of degenerative vascular changes, whenever and however observed. Such evidence includes: (1) signs of sclerosis seen in the eye grounds, (2) severely reduced dorsalis pedis artery pulsations observed by palpation and recorded by graphic tracings using a tambour cuff, (3) calcified plaques seen in the aorta on chest films, (4) electrocardiographic evidence of myocardial damage occurring in younger men, (5) a good history or signs of recent cerebral vascular accidents, and (6) evidence of Parkinsonism.

"Abnormal blood pressure" refers to a fixed arbitrary standard by which syphilitic and nonsyphilitic patients could be easily compared. Any patient with a systolic reading above 150 mm. Hg and/or a diastolic reading above 90 mm. Hg was arbitrarily considered "abnormal" for Table III.

Complaints of dyspnea were much more frequent than complaints of angina; the degree of dyspnea usually being mild ("short-winded after climbing two or three flights of steps").

"Arthritis" was symptomatic primarily, although many cases were substantiated by visible changes in the extremities or by x-ray evidence.

"Strokes" were recorded whenever neurologic evidence supported the history given by the patient. Three cerebrovascular accidents which occurred among men less than 60 years of age were among syphilitic patients.

In summary, Table III shows 4 cardiovascular features in which the syphilitic patients suffer by comparison with the nonsyphilitic. Each of the 4 differences is statistically significant at the 5 per cent level of significance. At this point, it is well to reiterate that this is a study of Negro males, of whom it has been said that the cardiovascular system is peculiarly susceptible to attack by the *Treponema pallidum*.[9]

NEUROLOGIC FINDINGS

A neurologic examination was a part of the general physical examination and included an estimation of mental status, deep and superficial reflexes, examination of optic discs, coordination, gait and speech, motor and sensory functions, cranial nerves, pupillary responses, and Romberg and Babinski signs. In the

Our conclusion from the findings in this examination suggest that although it is not possible to ascribe electrocardiographic abnormalities to the syphilitic process alone, it is possible that the excess of abnormal findings in the syphilitic group may represent an undefined effect of the specific disease factor.

CLINICAL ABNORMALITIES

Under the general heading of clinical abnormalities are grouped various features of the medical history and physical examination. The results of this comparison are shown in Table III, which for convenience is divided into two parts, showing abnormalities which proved to be significantly different in their occurrence among the syphilitic and nonsyphilitic patients, and those conditions for which significant differences could not be established. Most of the signs and symptoms considered in this table are concerned with the cardiovascular system. This indicates not so much that our attention was focused on cardiovascular changes, but rather that relatively simple methods for recording and measuring cardiovascular abnormalities were more readily available than tests of other systems, e.g., central nervous system.

TABLE III. THE COMPARATIVE INCIDENCE OF CLINICAL ABNORMALITIES AMONG SYPHILITIC AND NONSYPHILITIC GROUPS

ABNORMALITIES	PATIENT STATUS			
	SYPHILITIC (139)		NONSYPHILITIC (93)	
	NO.	PER CENT	NO.	PER CENT
A. Abnormalities found to be significantly greater among the syphilitic group				
Cardiac—chief complaint	32	23.0	7	7.5
Cardiac enlargement	89	64.0	44	47.3
Arteriosclerosis	100	71.9	47	50.5
"Abnormal" blood pressure (systolic 150 and/or diastolic 90)	81	58.3	31	33.3
B. Abnormalities not significantly greater among the syphilitic group				
Angina	32	23.0	17	18.3
Dyspnea	71	51.1	40	43.0
Symptomatic arthritis	74	53.2	48	51.6
Strokes (cerebrovascular accidents)	4	2.9	3	3.2
Deafness (partial or total)	12	8.6	8	8.6
Impaired vision (nonsyphilitic)	8	5.8	7	7.5

Differences in the incidence of abnormalities in the two groups were considered to be significant where the t-value was 2.0 or more, or at the 5 per cent level of significance.

First, only 232 of the 267 men examined in the survey are compared in this table. This is because most of the examinations done outside of Alabama by other examiners were omitted. It was felt that some of these clinical conditions

aging group of poor educational background, tests were purposely as simple and objective as possible. Although the range of normality was broad, abnormalities, when present, were striking and multiple and usually were associated with other signs.

LATE SYPHILIS

Among the 159 surviving syphilitic patients examined, 23 (14.5 per cent) showed evidence of late syphilis (Table IV). Eleven, or approximately half of these had signs of cardiovascular disease; other patients were about evenly divided between neurosyphilis and osseous syphilis. It is worth noting that the bulk of these patients were untreated and that no one patient with late syphilis had received an adequate course of therapy.

TABLE IV. EXTENT OF DEVELOPMENT OF LATE SYPHILIS BY TREATMENT STATUS IN LIVING SYPHILITIC PATIENTS AT THE TIME OF THE 1952 PHYSICAL EXAMINATION

LATE SYPHILITIC MANIFESTATION	NUMBER OF PATIENTS	UN-TREATED	PRACTI-CALLY UNTREATED	INADE-QUATELY TREATED	ADE-QUATELY TREATED
Paresis	1	—	—	1	—
Tabes	1	1	—	—	—
Optic atrophy	2	1	—	1	—
Tabes and optic atrophy	2	1	—	1	—
Aneurysm	3	2	1	—	—
Aortic regurgitation	5	4	—	1	—
Aneurysm and regurgitation	2	1	1	—	—
Tabes, optic atrophy, and aneurysm	1	—	—	1	—
Bone syphilis	6	3	1	2	—
All late syphilis (total)	23	13	3	7	—

DISCUSSION

Syphilis has indeed a serious adverse effect on the well-being of the group of individuals in whom the disease is allowed to progress with little or no treatment. The reduction in life expectancy which has been shown is in part based upon the fact that certain of the late complications of the disease either kill directly or are considered as primary causes of death as shown in members of syphilitic and control groups who have come to autopsy. Review of those still living (Table IV) reveals that an appreciable number have late complications of syphilis which probably will result, for some at least, in contributing materially to the ultimate cause of death. It is evident, though, that it is impossible in the case of the individual to predict whether the body will overcome the infection without treatment, or whether one of the late complications will develop. Indeed, it seems from consideration of the autopsy material that it is impossible during life to determine whether the untreated individual, seronegative or not, has chronic activity in the aorta as a result of the persistence of activity of *T. pallidum*.

It has been shown that in addition to specific marked changes related to syphilis, the syphilitic group also has an excess of abnormal findings not con-

sidered as directly related to syphilis. These findings cannot be explained, and the final interpretation of these data will have to be held in abeyance until the entire group has run the life span.

SUMMARY

This report is one of a series in a continuing study of untreated syphilis in the male Negro by the United States Public Health Service. The study consists of 600 men who have been followed clinically, serologically, and pathologically (to post-mortem examination in over 63 per cent of the deceased patients). This study is unique because of the inclusion of nonsyphilitic individuals of comparable ages to the syphilitic patients at the onset of the study; furthermore, these "controls" have been followed as intensively for the past twenty years as have the syphilitic men.

In this report, methods and problems in diagnosis of clinical syphilis are described as they were encountered in the collection of the statistical data obtained. Clinical findings are reported from physical examination, medical history, x-ray and fluoroscopy, serologic testing, electrocardiography, and neurologic examination; comparisons between syphilitic and nonsyphilitic individuals are shown usually by age groups; these comparisons have been subjected to statistical tests for significance.

1. Findings in this study seem to confirm the impression that, in male Negroes with untreated syphilis, the cardiovascular system frequently is involved.

2. Among the 23 living men who have developed some form of late syphilis, not one has received adequate therapy prior to the recent survey.

3. Problems of diagnosis of syphilis among the aged are complex, especially in evaluating findings related to the cardiovascular system.

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